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How to do it: Counselling patients with multiple sclerosis regarding stem cell ‘tourism’

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Abstract (150 words)

Given the intuitive potential of stem cell therapy and limitations of current treatment options for progressive multiple sclerosis (MS), it is perhaps unsurprising that patients consider undertaking significant clinical and financial risks to access stem cell transplantation. However, while there is increasing evidence to support autologous haematopoietic stem cell transplantation (AHSCT) in aggressive relapsing remitting MS, interventions employing haematopoietic or other stem cells should otherwise be considered experimental and can be recommended only in the context of a properly regulated clinical study. Understandably, neurologists may lack familiarity with AHSCT procedures and specific requirements for quality assurance and safety standards as well as post-procedure precautions and follow up. Consequently they may feel ill-equipped to offer advice to patients. Here, we highlight important points for discussion in consultations with patients considering stem cell 'tourism' for MS.

Introduction

Multiple Sclerosis (MS) is a chronic, immune-mediated, inflammatory disease of the central nervous system (CNS) causing demyelination and axonal loss with associated neurological disability. It affects approximately 100,000 people in the UK where it is the commonest cause of acquired neurological disability in young adults.[1] Although disease modifying treatments are available for patients with relapsing remitting MS, treatment options for patients with progressive disease are largely restricted to symptomatic therapies. Given the inadequacy of currently available treatment options, it is not surprising that patients with MS may seek experimental therapies and, if participation in regulated clinical trials is not possible or if they have firmly held views on the efficacy of a particular approach, they may explore alternative approaches.

Direct-to-consumer advertising of unproven interventions, and accessibility of information via the internet have increased patient demand, but there are increasing concerns, particularly with respect to clinical and financial risks presented to patients - not to mention the reputation of stem cell research.[2, 3] To date, efforts to regulate this global problem have met with little success[4] and, whilst patient autonomy must be respected, clinicians also have a responsibility to discuss potential risks, and advise patients against interventions considered inappropriate, unproven and potentially harmful. However, while neurologists may understand the level of evidence for stem cell therapy, they may be less familiar with procedures and risks associated with transplantation, and with internationally-agreed standards for transplant centres. Our aim is to provide practicing neurologists with an overview of the AHSCT process and a framework to assist when counselling patients considering stem cell 'tourism'.

Stem cell therapy for MS – what is the attraction?

In AHSCT, haematopoietic stem cells (HSC) rescue patients from fatal bone marrow failure (aplasia) induced by myeloablative chemotherapy or radiotherapy. In the context of MS, the rationale for this type of stem cell treatment is to permit exposure to powerful immunoablative therapies, 're-setting' the immune system. However, stem cell therapy has long been appreciated to hold promise for a wide range of conditions for which current treatments are sub-optimal or non-existent. The intuitive appeal of a ready source of cells

which can multiply, migrate and differentiate to repair damaged tissues has led to considerable hype and expectation[5] although, to date, stem cell therapy including AHSCT is integral to treatment of relatively few conditions outside haematology and oncology. More recently, research attention has shifted from a focus on the 'pluripotency' of stem cells to the potential benefit of harnessing non-canonical reparative properties including anti-inflammatory or immunomodulatory effects, neuroglial protective properties or angiogenesis. These functions may be effected *via* a range of mechanisms including paracrine activity and cell fusion.[6]

It should be noted however, that irrespective of the mechanism(s) of effect, numerous technical challenges remain to be solved before the full clinical impact of AHSCT or other stem cell-based interventions can be realised. While advances can be made in the context of well-regulated clinical research, the process will necessarily be iterative if excessive morbidity and mortality are to be avoided.[7]

Stem cell therapy

Clarification of what is meant by 'stem cell therapy' is critical to any discussion regarding potential risks and benefits. A full review of the important consideration of cell source and summary of current stage of clinical translation is outwith the current remit (recently reviewed[8]). In summary however, cells may be isolated from the patient (autologous) or donated by others (allogeneic) and specific cell type must be considered. In AHSCT, haematopoietic stem cells (HSC) are key but there is increasing appreciation that additional cell populations may have regenerative potential. These include mesenchymal stromal cells (MSC) isolated from bone marrow or other sources e.g. adipose tissue. MSC have many attractive properties for cell-based therapy[6] but, as yet, clinical benefit has not been demonstrated in randomised, placebo-controlled trials in neurological diseases including MS.

It is recognised that unscrupulous providers may target vulnerable patient populations marketing interventions that are unproven and potentially dangerous. This worldwide issue is proving difficult to regulate and requires ongoing collaboration between state regulators, patient advocacy groups, clinicians and scientists[9-11] but the importance of highlighting

to patients that regulated clinical research rarely, if ever, requires participants to pay for inclusion should not be underestimated.

AHSCT

AHSCT is a well-established therapeutic option in haemato-oncology. Replacing the haematological system goes hand in hand with regenerating a 'new' immune system, explaining its potential in auto-immune disease. However, treatment-related toxicity has restricted its use to only a small proportion of patients with highly aggressive, treatment-refractory diseases including systemic sclerosis and systemic lupus erythematosus.[12] The mechanism(s) by which AHSCT exerts clinical effects in MS is not entirely certain but is likely to involve immunomodulation in favour of regulatory cells with suppression of pro-inflammatory lymphocytes.[13]

Such 're-setting' must be preceded by attempts essentially to 'remove' the patient's original immune system ('conditioning') before transplantation, and so AHSCT can be broken down into stages: stem cell collection, graft preparation and storage, conditioning regimen, and transplant delivery and engraftment (figure 1).

HSC collection, graft preparation and storage

Prior to collection, patients for AHSCT should be screened for herpes simplex virus, varicella zoster virus, human immunodeficiency virus, and the hepatitides. Although HSC comprise some 0.01% of nucleated cells in the marrow, they can restore all blood lineages following myeloablation[14]. The key marker used in clinical practice to predict functional engraftment is the peripheral CD34-positive cell count with a requirement for $2-3 \times 10^6$ CD34-positive cells/kg body weight.[15] Until recently, autologous or allogeneic cells were isolated by bone marrow harvest involving multiple transcortical punctures of bone, usually posterior iliac crest, and aspiration of marrow under general anaesthesia. Increasingly however, cytokine-mediated mobilisation of cells into peripheral blood using low dose chemotherapy, granulocyte colony stimulating factor (G-CSF) and/or stem cell factor (SCF) followed by apheresis is employed. Unexpectedly, use of G-CSF alone may be associated with an MS flare, so it is frequently used in combination with corticosteroid therapy or cyclophosphamide.[16] Umbilical cord blood is an alternative cell source;

although the low CD34-positive cell dose previously restricted use of cord blood to children, outcomes in adults are now improving.[17]

Following collection, cells may be stored without manipulation or be T cell depleted with the aim of further reducing autoreactivity following engraftment.[14, 18] Although HSC can be infused fresh, they are more commonly cryopreserved for storage.

Conditioning regimen

Patients undergoing AH SCT are exposed to a conditioning regimen designed to either eradicate malignant cells or to eliminate autoreactive cells in autoimmune diseases. The conditioning regimen is classified as 'high', 'intermediate' or 'low' intensity according to the degree of myeloablation; this predicts to a large degree the procedure-associated risk and morbidity. 'High' intensity regimens may include total body irradiation and/or myeloablative chemotherapy, frequently in combination with immune-depleting drugs such as anti-thymocyte globulin, alemtuzumab or rituximab to further suppress autoreactive cells.[18] These are associated with improved outcomes in preclinical studies but increased transplant-related mortality in patients.[19, 20] 'Low' intensity regimens aim for lymphoablation only but may be of limited long-term efficacy. In European studies, the most frequently employed regimen is 'BEAM' - an 'intermediate' intensity regimen including carmustine, etoposide, cytarabine and melphalan, often followed by anti-thymocyte globulin.[16]

Transplant delivery and engraftment

The HSC source is infused intravenously following exposure to the conditioning regimen and functional engraftment is expected to occur in approximately 2 weeks. Longer term immunological changes include a sustained inversion of CD4/CD8 ratio[21] and a broader clonal diversity in T cell receptor repertoire potentially making patients susceptible to opportunistic infections such as *Pneumocystis jirovecii* pneumonia,[22] although many centres recommend routine prophylaxis only while the CD3 lymphocyte count is $<300 \times 10^6$ cells/L. Post-transplantation, regular monitoring of full blood count including lymphocytes should be undertaken for at least 2 months to ensure sustained myeloid and platelet engraftment, and there should be a low index of suspicion to consider re-screening for herpes simplex virus, varicella zoster virus, human immunodeficiency virus if relevant symptoms emerge at any time point post-transplantation.

AHSCT for MS – what are the risks?

The source and processing of cells for transplantation are critical determinants of the likely safety of the approach and each has potential advantages and disadvantages. With respect to specific risks of transplantation, autologous therapies are not associated with risks of immunosuppression or graft versus host disease which may complicate allogeneic transplants but autologous cells may have inherent deficits associated with either MS or its comorbidities.[23, 24] Additional risks include those associated with a bone marrow harvest performed under general anaesthetic or an MS flare following administration of a bone marrow mobilising agent. Furthermore, manipulation of cells *ex vivo* may be complicated by infection or cell transformation due to induction of genetic instability. Rarely, reactions to chemicals such as dimethyl sulfoxide (DMSO) used in cryopreservation may cause anaphylaxis.

Overall however, the greatest risks are associated with myeloablative procedures due to neutropenic sepsis and haemorrhage in the context of thrombocytopenia; these contribute disproportionately to the estimated 2-3% risk of transplant-related mortality associated with AHSCT.[25] In general, patients with MS face similar regimen-related risks as patients undergoing transplantation for other indications but a number of complications are recognised to occur either more frequently or with greater severity including increased incidence of urinary tract infections, transient worsening of MS-related symptoms due to febrile neutropenia or infection (pseudorelapse), reactivation of human herpes viruses following CD34 selected grafts or anti-thymocyte globulin treatment as well as the additive effect on disability of neurotoxic conditioning regimens.[18] Late complications also include development of secondary autoimmunity; approximately 9% in all patients treated with autologous AHSCT for autoimmune disease.[26] Rituximab may be given concomitantly although can be associated with serious infections including viral reactivation and progressive multifocal leukoencephalopathy, albeit rarely.[27]

Key consideration for patients considering health ‘tourism’

Given the significant risks of morbidity and mortality, AHSCT for patients with MS can, at present, be recommended only in the context of a properly regulated clinical study or trial.

Patients must also consider potential implications of travelling in the immediate period following myeloablative procedures when they may be thrombocytopenic or significantly immunosuppressed. Furthermore, AHSCT or involvement in unregulated experimental procedures is highly likely to disbar patients from future participation in clinical trials.

The degree of regulation to which transplant centres are subject varies around the world but patients should be aware that internationally-agreed standards exist. Centres conducting AHSCT should have accreditation with the International Society for Cellular Therapy (ISCT) and the European Society for Blood and Marrow Transplantation (EBMT) via the Joint Accreditation Committee (JACIE). Outcome data should be reported to EBMT or another transplant registry. An additional transplant centre consideration is whether they are aware of specific needs and risks faced by those with MS; outcomes are likely to be better in those centres with greater familiarity treating patients with MS.[18]

For those determined to travel to access AHSCT offered on a commercial basis, we recommend they review the provider's reputation and safety record with care. We advise review of the EBMT/JACIE patient guidance[28, 29] and our additional recommendations are:

1. The centre must have JACIE accreditation and it is essential that outcome data are reported to EBMT or another transplant registry. The experience of the centre in treating patients with MS should be noted.
2. Transplant centres must perform a rigorous pre-transplant assessment of the individual's suitability and fitness for the procedure and discuss any procedure-associated risks in the context of MS and additional co-morbidities.
3. The patient should check in advance whether the clinic is adequately prepared to handle emergencies such as a serious allergic reaction or cardiac arrest, and enquire about contingency plans should complications occur.
4. Transplant centres must provide recommendations regarding post-procedure travel arrangements in advance of treatment and agree to issue a discharge summary to the regular care provider including details of the conditioning regimen and cell infusion as well as any complications encountered.
5. Specific requirements for follow up and monitoring must be provided by the transplant centre together with information regarding potential risks of treatment in the immediate future and longer term.

For patients considering other stem cell ‘treatments’, inclusion can only be recommended in the context of a regulated clinical trial and particular caution is required when participants are required to pay for an intervention that is not approved by the relevant national regulatory authority.

Conclusions

The frustration experienced by patients with MS in the context of slow progress with the development of novel and effective treatments, particularly for progressive disease, is understandable. However, the urge to ‘do something’ can encourage people to consider unproven interventions of uncertain benefit despite their often-significant risk profile which may include death and worsening disability. Wherever possible, patients should be encouraged to participate in well-regulated, carefully conducted clinical trials and registry studies where adverse events are closely monitored and where both adequate clinical back-up should complications be encountered and good follow up care are available. Ultimately, trials will establish whether AHSCT is effective and will inform improvements in both the procedure and patient selection. Patients who can consent to travel for the purpose of accessing direct-to-consumer treatments of uncertain benefit should be carefully advised of the potential risks, preferably in writing and, where there are concerns regarding capacity for consent, safeguarding measures should be taken.

Key points

1. AHSCT carries risk of significant morbidity and mortality in patients with MS, the more so when conducted in centres outside internationally agreed regulatory processes. It can be considered in the context of aggressive relapsing and remitting MS but the benefit of AHSCT is far from clear in progressive MS
2. Those patients who pursue AHSCT on a direct-to-consumer basis, should ensure that the centre conforms to internationally-agreed standards
3. Due care must be given to travel arrangements and follow up post-procedure, particularly for those who have received myeloablative conditioning regimens
4. Aside from AHSCT in carefully defined circumstances and settings, no form of stem cell ‘treatment’ for MS can be recommended at present outside the context of a

properly regulated clinical trial and participants should not be expected to pay for inclusion.

Figure Legends

Figure 1 Autologous haematopoietic stem cell transplantation

Schematic illustrating stages of AHSCT including mobilisation, collection, conditioning, storage and infusion.

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